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REMARKS/ARGUMENTS

The concentration of benzalkonium chloride (BAK) recited in present claim 2 is combined into present claim 1 and the concentration of BAK recited in present claim 6 is combined into present claim 5.

Claims 4 and 8 (should be all Claims) are rejected as unpatentable over Dean (US 6,166,073) in view of JP Patent Abstract and Helberg (US 6646001).

Present Invention

The present inventors first confirmed the problem of white turbidity due to a change of formulation (complex formation - see specification page 3, last paragraph) in ophthalmic solutions containing latanoprost at a certain concentration (0.005 to 0 .01 % (W/V)) and BAK at a certain concentration (0/003 to 0.01 % (W/V)), and then found means of

1) using BAK represented by the formula of $[C_6H_5CH_2N(CH_3)_2R]Cl$ (wherein R is alkyl having 12 carbon atoms) as the preservative, and/or

2) adding a tonicity agent consisting essentially of a nonionic tonicity agent, thereby solving the problem.

As described in the present specification, white turbidity, which is a problem to be solved in the present invention, is observed in the case where latanoprost at the above-mentioned concentration and BAK at the above-mentioned concentration exist in the solutions, and is not observed

under conditions other than the above (see the present Specification page 3, line 13 to page 4, line 7).

Cited References

Dean et al (U.S. Patent 6,166,073) describe compositions containing DP-agonist and FP-agonist prostaglandin agonists for treating glaucoma or ocular hypertension. However, Dean et al do not describe or suggest at all ophthalmic solutions containing latanoprost and benzalkonium chloride both having the concentrations where white turbidity is observed. From this fact, it is submitted that one cannot recognize the problem to be solved by the present invention from Dean et al or the solution to the problem which is the present invention.

Combining the Patent Abstract of Japan with Dean et al does not describe or suggest at all latanoprost. Therefore, the skilled person cannot possibly recognize the problem to be solved by the present invention from the Patent Abstract of Japan.

Hellberg et al (U.S. Patent 6,646,001) describe compositions for the treatment of glaucoma and ocular hypertension, comprising a prostaglandin FP receptor agonist and a prostaglandin synthesis inhibitor. However, Hellberg et al do not describe or suggest ophthalmic solutions containing latanoprost and benzalkonium chloride both having the concentrations where the white turbidity is observed. From this fact, it

is submitted that the skilled person cannot recognize the problem to be solved by the present invention from Hellberg et al, alone or in combination with the other art.

As discussed above, ophthalmic solutions containing latanoprost having the above-mentioned concentration and BAK having the above-mentioned concentration is not described in any of the cited references. It is therefore impossible even for the skilled person to recognize the problem to be solved by the invention from any of the cited references. That is, from the cited references where the problem to be solved by the present invention is not described, it is impossible even for the skilled person to conceive of an ophthalmic solution problem and the method according to the present invention that solved the problem. Therefore, the present invention as now claimed is not shown or suggested by the combined art.

Advantageous Effects of the Present Invention

The Examiner raised a question of evidence of a special effect. This is provided in the specification as filed.

In the present invention, in order to prevent the white turbidity due to a change of formulation in ophthalmic solutions, the following means are used:

1) using BAK wherein alkyl has 12 carbon atoms, and/or

2) adding a tonicity agent consisting essentially of a nonionic tonicity agent.

Regarding means 1), (BAK having 12 carbon atoms is used). Since none of the references even describe the problem of white turbidity, let alone BAK having 12 carbon atoms, it is impossible to lead from the references to the ophthalmic solutions wherein benzalkonium chloride having 12 carbon atoms in the alkyl is used as a means for solving the problem. Moreover, the present invention according to means 1) exhibits a novel effect of preventing white turbidity, which is not a problem to be solved in the references but in the present invention, and therefore, such an effect can not be obvious from the references where even the problem of white turbidity is not described. Hence, the ophthalmic solution formulated according to means 1) (BAK with 12 carbon alkyl) of the present invention exhibits a novel effect, or an unexpected effect and it is not obvious from the art.

Regarding means 2), by adding a tonicity agent consisting essentially of a nonionic tonicity agent white turbidity due to a change of formulation is prevented. The tonicity agent is introduced, following the inventor's focus on the fact that the use of the salts as a tonicity agent was a cause of white turbidity. Accordingly, it is impossible to lead from the references to the ophthalmic solution wherein a

tonicity agent consisting essentially of a nonionic tonicity agent is added as a means for solving the problem. Moreover, the present invention according to means 2) exhibits a novel effect of preventing white turbidity, which is not a problem to be solved in the references but in the present invention, and therefore, such an effect cannot be obvious from the references where even the problem of white turbidity is not described. Hence, an ophthalmic solution formulated according to means 2) of the present invention exhibits a novel effect and is not shown or suggested by the art combination.

Data showing unexpected results

The Examiner stated that the advantageous effect due to BAK having 12 carbon atoms is not described in the present specification. However, such an effect is clear from Examples (Tables 1, 3, 5, and 7) in the present specification, and therefore is clearly supported by the description of the present specification. Comparing comparative formulation 3 in Table 1 with formulation 4 in Table 3, it can be seen that all the components and their concentrations are the same except for the difference in that BAK is used in comparative formulation 3 while BAK C_{-12} is used as a preservative. The same is equally true of the case of comparative formulation 4 in Table 1 and formulation 5 in Table 3.

Here, BAK used in comparative formulations 3 and 4 is a

mixture which has the chemical structure represented by [C6H5CH2N(CH3)2R]Cl wherein R is alkyl having 8 to 18 carbon atoms , while BAK C-12 used in formulations 4 and 5 is a non-mixture which has the chemical structure represented by [C6H5CH2N(CH3)2R]Cl wherein R is alkyl having 12 carbon atoms only. According to the United States Pharmacopeia, copy of a relevant page of which is attached hereto as a reference material, it is stated that R represents a mixture of alkyls including long chain of C8 or more, and that alkyls including C12, C14, and C16 comprises the major portion.

Next, comparison of appearance and residual ratio between Tables 5 and 7 reveals that white turbidity is observed and the residual ratio is below 70% in comparative formulation 3, while white turbidity is not observed (colorless and transparent) and the residual ratio is extremely high (97.3%). Likewise, also in the case of comparative formulation 4 and formulation 5 reveals the similar results. Accordingly, from the results obtained in Tables 5 and 7, it can be confirmed that the advantageous effect that white turbidity in the aqueous solution is prevented and the high residual ratio of latanoprost is obtained by changing BAK wherein R represents a mixture of alkyls having various length, to BAK C_{12} wherein R represents a non-mixture of alkyls having 12 carbon

atoms. In other words, Tables 5 and 7 clearly shows the advantageous effect exhibited by BAK C_{12}, and such an effect is clearly described in the present specification.

The present specification also describes the advantageous effect obtained by adding a tonicity agent consisting essentially of a nonionic tonicity agent. In comparative formulation 3 in Table 1, as a tonicity agent, sodium chloride which is an ionic tonicity agent is added. On the other hand, In formulations 6 to 10 in Table 4, as a tonicity agent, a nonionic tonicity agent is added. Other components and their concentrations are the same in comparative formulation 3 and formulations 6 to 10.

Next, comparison of appearance and residual ratio between Tables 5 and 8 reveals that white turbidity is observed and the residual ratio is below 70% in comparative formulation 3, while white turbidity Is not observed (colorless and transparent) and the residual ratio Is extremely high (94.6 to 98.6%). Accordingly, from the results obtained in Tables 5 and 8, it can be confirmed the advantageous effect that white turbidity in the aqueous solution is prevented and the high residual ratio of latanoprost is obtained by adding a tonicity agent consisting essentially of a nonionic tonicity agent. In other words, Tables 5 and 8 clearly shows the advantageous effect exhibited by adding a

tonicity agent consisting essentially of a nonionic tonicity agent, and such an effect is clearly described in the present specification.

Conclusion

As discussed above, it is impossible to arrive at the ophthalmic solution according to the present invention from a combination of the references where the problem to be solved by the invention is neither described nor suggested. Moreover, the ophthalmic solution according to the present invention possesses a novel effect that the problem of white turbidity which was not known before the present invention disclosure, is solved, or an unexpected effect. Therefore, the present invention as claimed is patentable over the cited art, alone or in combination.

In view of the above, the rejections are avoided. Allowance of the application is therefore respectfully requested.

Respectfully submitted,

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THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

omophenol blue TS, and titrate the liberated hydrochloric acid 1 N sodium hydroxide VS to a light-green endpoint. Perform a determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). mL of 1 N sodium hydroxide is equivalent to 106.1 mg of O.

mpound Benzaldehyde Elixir

ompound Benzaldehyde Elixir contains 0.05 percent zaldehyde in a suitably flavored and sweetened alcoholic vehicle.

aging and storage—Preserve in tight, light-resistant contain-

hol content, *Method I* ⟨611⟩: between 3.0% and 5.0% of OH.

anic volatile impurities, *Method I* ⟨467⟩: meets the require- nts.

(Official until July 1, 2007)

nzalkonium Chloride

monium, alkyldimethyl(phenylmethyl)-, chloride.
ylbenzyldimethylammonium chloride [8001-54-5].

enzalkonium Chloride is a mixture of alkylbenzyl- ethylammonium chlorides of the general formula:

$$[C_6H_5CH_2N(CH_3)_2R]Cl$$

which R represents a mixture of alkyls, including all some of the group beginning with n-C_8H_{17} and nding through higher homologs, with n-$C_{12}H_{25}$, n-H_{29}, and n-$C_{16}H_{33}$ comprising the major portion. On anhydrous basis, the content of the n-$C_{12}H_{25}$ olog is not less than 40.0 percent, and the content n-$C_{14}H_{29}$ homolog is not less than 20.0 percent, of tal alkylbenzyldimethylammonium chloride con- . The amounts of the n-$C_{12}H_{25}$ and n-$C_{14}H_{29}$ olog components comprise together not less than percent of the total alkylbenzyldimethylammonium oride content. The total alkylbenzyldimethylammo- m chloride content, calculated on the anhydrous is, allowance being made for the amount of residue ignition, is not less than 97.0 percent and not more 103.0 percent of $[C_6H_5CH_2N(CH_3)_2R]Cl$.

aging and storage—Preserve in tight containers.
Reference standards ⟨11⟩—*USP Benzalkonium Chloride RS*.
ification—

: To a solution (1 in 100) add 2 N nitric acid or mercuric ride TS: a white precipitate is formed, and it is soluble in ohol.

: Dissolve about 200 mg in 1 mL of sulfuric acid, add 100 mg odium nitrate, and heat on a steam bath for 5 minutes. Cool, te with water to 10 mL, add 500 mg of zinc dust, and warm for 5 utes on a steam bath. To 2 mL of the clear supernatant add 1 mL odium nitrite solution (1 in 20), cool in ice water, then add 3 mL solution of 500 mg of 2-naphthol in 10 mL of 6 N ammonium roxide: an orange-red color is produced.

C: A solution of it in a mixture of equal volumes of water and alcohol responds to the tests for *Chloride* ⟨191⟩.

Water, *Method I* ⟨921⟩: not more than 15.0%.

Residue on ignition ⟨281⟩: not more than 2.0%.

Water-insoluble matter—A solution (1 in 10) is free from turbidity and insoluble matter.

Limit of foreign amines—To 5 mL of a solution (1 in 50) add 3 mL of 1 N sodium hydroxide: no precipitate is formed. Heat to boiling: the odor of amines is not perceptible.

Ratio of alkyl components—

Mobile phase—Adjust a 0.1 M solution of sodium acetate with glacial acetic acid to a pH of 5.0. Mix 55 parts of this solution with 45 parts of acetonitrile, filter, and degas. The acetonitrile concentration may be varied from 40 parts to 60 parts to meet system suitability requirements.

Standard solution—Dilute USP Benzalkonium Chloride RS with water to obtain a solution having a known concentration of about 4 mg per mL.

Test solution—Dissolve about 1 g of Benzalkonium Chloride, accurately weighed, in water in a 50-mL volumetric flask, dilute with water to volume, and mix. Pipet 5.0 mL of this solution into a 25-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L10. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the resolution, *R*, between the C_{12} and C_{14} peaks is not less than 1.5; the column efficiency, determined from the C_{12} peak, is not less than 1000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0% determined from the C_{12} peak.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas. Identify the homolog peaks by comparison of the retention times with those from the *Standard solution*, similarly chromatographed. Calculate the percentage of each quaternary ammonium homolog taken by the formula:

$$100(A/B)$$

in which A is the product of the area obtained from the homolog multiplied by its molecular weight; and B is the sum of all of these products. The molecular weights of the C_{10}, C_{12}, C_{14}, and C_{16} homologs are 312, 340, 368, and 396, respectively.

Assay for total alkylbenzyldimethylammonium chlorides—Weigh accurately a quantity of Benzalkonium Chloride equivalent to about 500 mg of anhydrous benzalkonium chloride, and transfer, with the aid of 35 mL of water, to a glass-stoppered, 250-mL conical separator containing 25 mL of chloroform. Add 10.0 mL of freshly prepared potassium iodide solution (1 in 20), insert the stopper in the separator, shake, allow the layers to separate, and discard the chloroform layer. Wash the aqueous layer with three 10-mL portions of chloroform, and discard the washings. Transfer the aqueous layer to a glass-stoppered, 250-mL conical flask, and rinse the separator with three 5-mL portions of water, adding the washings to the flask. Add 40 mL of cold hydrochloric acid to the flask, mix, and titrate with 0.05 M potassium iodate VS until the solution becomes light brown in color. Add 5 mL of chloroform, insert the stopper into the flask, and shake vigorously. Continue the titration, dropwise, with shaking after each addition, until the chloroform layer becomes colorless and the aqueous layer is clear yellow. Perform a blank determination, using 20 mL of water as the sample. The difference between the two titrations represents the amount of potassium iodate equivalent to the weight of benzalkonium chloride in the sample. Each mL of 0.05 M potassium iodate is equivalent to $x/10$ mg of benzalkonium chloride, where x represents the average molecular weight of the sample, derived by summing, for all homologs, the products

$$W(A/B)$$

where W is the molecular weight of a given homolog, A is the area of the peak produced by that homolog in the chromatogram from the *Ratio of alkyl components* test, and B is the total peak area for all homologs in that chromatogram.